IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re PATENT APPLICATION OF

Robert B. DICKSON *et al.*

Application No. 09/936,333

Filed: March 5, 2002

Examiner: Zachariah Lucas

Group Art Unit: 1648

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BRIEF ON APPEAL

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I. INTRODUCTION

This appeal is from an official action mailed August 10, 2005, finally rejecting claims 15, 16, 18, 19, and 34-36 of the above-identified patent application.

A. Real Party in Interest

The real party in interest for this appeal and the present application is the Georgetown University School of Medicine, by way of an Assignment recorded in the U.S. Patent and Trademark Office at Reel 012770, Frame 0529.

B. Statement of Related Appeals and Interferences

There are presently no appeals or interferences known to Appellants, the Appellants' representatives or the Assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

C. Status of Claims

Claims 15, 16, 18, 19, and 34-36 are pending. Claims 15 and 19 are allowed, and claims 16, 18, and 34-36 stand rejected and are on appeal. The claims on appeal are set forth in the attached Appendix A. Claim 16 is independent, and claims 18, and 34-36 depend from claim 16.

D. Status of Amendments Filed Subsequent to Final Rejection

An amendment under 37 C.F.R. §1.116 was filed November 8, 2005, in response to the final official action mailed on August 10, 2005. The advisory action mailed November 30, 2005, indicated that for purposes of appeal, the amendment filed November 8, 2005, would be entered of record, and that claims 15 and 19 would be allowed, and claims 16, 18, and 34-36 would remain rejected.

II. SUMMARY OF THE CLAIMED INVENTION

A. Overview

The applicants have discovered that human matriptase, a serine protease enzyme associated with tumor growth and invasion, is converted from an inactive single-chain form (zymogen) to a proteolytically active, two-chain form, by cleavage at a specific site within the matriptase polypeptide. Prior to the applicants' discovery, the active, 2-chain form of matriptase

had not been isolated, described or characterized. The applicants have characterized the active, two-chain form of the enzyme by describing its amino acid sequence and the location of the site of cleavage that activates the enzyme, and by demonstrating that Hepatocyte Growth Factor Activator Inhibitor-1 (HAI-1) binds to the two-chain form of matriptase and inhibits the active protease, but does not bind to the inactive, single-chain form. The applicants have further demonstrated the production and identification of hybridomas that make monoclonal antibodies that specifically recognize and bind to the active two-chain form of human matriptase as their antigen, and have negligible affinity for the single-chain form of matriptase. Prior to the applicants' discovery, it was not known that matriptase is produced by human cells as an inactive single-chain polypeptide that is cleaved to form a proteolytically active two-chain form of matriptase, nor was it known that monoclonal antibodies could be prepared and identified that are capable of binding specifically to the two-chain form of matriptase as their antigen, and have negligible affinity for the inactive, single-chain form of matriptase.

B. Object of the Invention

It is an object of the invention to provide antibodies that bind specifically to the two-chain form of human matriptase and have little or no affinity for the single-chain form of matriptase.

C. Embodiment of the Invention

The application describes a method for preparing monoclonal antibodies that are capable of binding to the two-chain form of human matriptase as their antigen, *i.e.*, they bind specifically to the active, two-chain form of human matriptase and have little or no affinity for the inactive, single-chain form of human matriptase. The application describes (a) preparing hybridomas that produce monoclonal antibodies that bind to the two-chain form of matriptase, and (b) screening the hybridomas to identify hybridomas that produce antibodies that have little or no affinity for the single-chain form of matriptase. The application demonstrates that a screen of about 80 hybridomas that produce monoclonal antibodies that bind to the two-chain form of human matriptase resulted in selection of two hybridomas (M69 and M123) that produce antibodies that are capable of binding specifically to the antigenic two-chain form of matriptase, and do not bind to the single-chain form of matriptase (*see* Example 5, pages 89-91).

The claims that stand rejected and are on appeal are directed to such antibodies that recognize and bind specifically to the two-chain form of matriptase but not the single-chain form of matriptase. In particular, independent claim 16 of the present application is directed to "[a]n isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human." Claims 18 and 34-36 depend from claim 16. Claim 36 is directed to "[t]he antibody or immunologically reactive fragment thereof of claim 16, which binds to the two-chain (active) form of a matriptase protein that is present in a complex comprising HAI-1 or a fragment thereof."

III. GROUNDS OF REJECTION TO BE REVIEWED

The official action of August 10, 2005, has rejected claims 16, 18, and 34-36 under 35 U.S.C. §112, first paragraph, for an alleged lack of written description of the claimed invention.

In the statement of the rejection in the final official action, the examiner alleged that written description is lacking because the application discloses two examples of antibodies that bind to the two-chain human matriptase with greater affinity than to the single chain form (M123 and M69), but "has not provided any means of determining what the epitope[s] these antibodies target so as to allow those in the art identify and particular structure (sic) that may be targeted which structure would correspond to an epitope present in the two-chain but not in the zymogen form of matriptase." *See* page 7 of the official action.

The examiner further rejected claim 36 under 35 U.S.C. §112, first paragraph, for alleged lack of written description. Claim 36 depends on claim 16, and further specifies an antibody that binds with greater affinity to the two-chain form of a matriptase protein that is present in a complex comprising HAI-1. The examiner acknowledged that antibody M123 is an example of an antibody according to claim 36, but alleged that the disclosure of one example of such an antibody is insufficient to support generic claim 36, for reasons similar to those given for the rejection of claim 16.

The examiner further rejected claims 16, 18, and 34-36 under 35 U.S.C. §112, first paragraph, for a lack of written description, because the application does not provide

reproducible means for producing disclosed monoclonal antibodies M123 and M69. This ground for rejection is overcome by the response to the final official action filed on November 8, 2005, which included a declaration that hybridomas that produce antibodies M123 and M69 have been deposited under the terms of the Budapest Treaty, and which amended the specification to provide the information regarding the deposit.

In the final official action, the examiner further rejected claim 36 under 35 U.S.C. §112, first paragraph, because the application was not considered to provide adequate description of a two-chain form of a matriptase protein in a complex with any Kunitz-type inhibitor other than HAI-1. This ground for rejection is overcome by the response to the final official action filed on November 8, 2005, which amended claim 36 to specify a complex comprising the two-chain form of a matriptase protein and HAI-1.

Thus, the issue on appeal is whether the specification, through (1) its disclosure and description of the structures and functional activities of the single-chain and two-chain forms of matriptase, (2) its disclosure that antibodies can be obtained that are capable of binding specifically to the two-chain form of matriptase and have negligible binding affinity for the single-chain matriptase protein, (3) its description of a method by which such antibodies can be prepared and identified, and (4) its description of preparing of two working examples of antibodies that are capable of binding specifically to different structural features on the antigenic two-chain form of matriptase with high affinity, and have little or no affinity for the single-chain form of matriptase, satisfies the requirements of 35 U.S.C. §112, first paragraph, for written description of the claimed invention.

IV. ARGUMENT

The examiner has acknowledged that the specification describes a reproducible method for obtaining antibodies of the claimed invention, and identifies two working examples of the claimed antibodies, but has rejected claims 16, 18, and 34-36 under 35 U.S.C. §112, first paragraph, for alleged lack of written description, because the claims describe the claimed antibodies in functional terms, and the application does not identify specific epitopes on the two-chain form of human matriptase that are recognized by the claimed antibodies.

The applicants respectfully submit that the application describes the antibodies to which claims 16, 18, and 34-36 are directed in a manner that satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the claimed antibodies.

The amount and type of information required to satisfy the requirement for written description for a claimed invention under 35 U.S.C. §112, first paragraph, is dependent on the nature of the invention. *See* In re Smyth, 178 U.S.P.Q. 279 at 284 (CCPA 1973). With respect to claims directed to antibodies, it is established that the requirement for written description under 35 U.S.C. §112, first paragraph, for claims directed to antibodies that bind to a well-characterized antigenic protein can be satisfied solely by description of the antigenic protein with reference to such distinguishing parameters as the molecular weight and/or the amino acid sequence of the antigenic protein.

> "In its Guidelines [regarding the requirement for written description under 35 U.S.C. §112, first paragraph], the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics... *i.e.,* complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure,* or some combination of such characteristics." *Guidelines,* 66 Fed. Reg. at 1106 (emphasis added). For example, the PTO would find compliance with 112, 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature. Synopsis of Application of Written Description Guidelines, at 60, *available at* http://www.uspto.gov/web/patents/guides.htm (*Application of Guidelines*)."

Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964 (Fed. Cir., 2002). Moreover, the PTO routinely issues patents with claims directed to antibodies that bind specifically to an antigenic protein that is disclosed and characterized by the corresponding application specifications, without requiring identification of the specific epitopes on the protein that are bound by the claimed antibodies, or without even requiring a demonstration that the claimed antibodies have been produced. The PTO's Written Description Guidelines, the examining practice of the PTO,

and the Court of Appeals of the Federal Circuit, have recognized that in view of the well defined structural characteristics of antibodies, the functional characteristics of antibody binding, and the developed and mature state of antibody technology, an application that describes and fully characterizes an antigenic protein in structural and chemical terms satisfies the written description requirement of 35 U.S.C. §112, first paragraph, with respect to claims directed to antibodies that bind specifically to the characterized antigenic protein.

In the present application, the applicants have disclosed and characterized an antigenic protein, the active, two-chain form of human matriptase, in terms of its amino acid sequence (SEQ ID NO: 4) and the location of the site of cleavage that activates the enzyme (*e.g.*, *see* Figs. 9 and 10). The application further demonstrates that HAI-1 binds to and forms a complex with the two-chain form of matriptase, but does not bind to the single-chain form of human matriptase. Furthermore, the specification describes reliable screening and assay procedures by which one of skill in the art can identify hybridoma clones that produce the claimed antibodies that bind specifically to the antigenic two-chain form of human matriptase and have little or no binding affinity for the single-chain form of matriptase. Moreover, the specification describes a working example in which approximately 80 hybridoma clones were screened using the disclosed method to obtain two disclosed hybridoma clones, M69 and M123, that produce antibodies of the claimed invention that bind specifically to the antigenic two-chain form of human matriptase without binding to the single-chain form of the protein. Differences in binding affinity of M69 and M123 for the non-boiled and boiled 95 kDa complex of HAI-1 and matriptase indicate that the two antibodies bind to different structural features on the antigenic two-chain form of matriptase. *See* Example 5, pages 89-91. The allegation in the statement of the rejection (page 8) that the application discloses only a single example of the antibody of claim 36 is incorrect. Since the hybridomas that were screened in Example 5 were generated using the 95 kDa complex of HAI-1 and the two-chain form of human matriptase as immunogen, both M69 and M123 antibodies bind to the two-chain (active) form of human matriptase protein that is present in a complex comprising HAI-1.

The representative number of species within a genus of a claimed invention that must be disclosed to satisfy the requirement for written description under 35 U.S.C. §112, first paragraph, depends on the nature and predictability of the field of the invention (*see* Regents of the

University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). As discussed above, decisions by the Court of Appeals of the Federal Circuit and PTO practice evidence a recognition that in view of the well defined structural characteristics of antibodies, the functional characteristics of antibody binding, and the developed and mature state of antibody technology, an application that describes and fully characterizes an antigenic protein in structural and chemical terms satisfies the written description requirement of 35 U.S.C. §112, first paragraph, with respect to claims directed to antibodies that bind specifically to the characterized antigenic protein, even if the claimed antibodies have not been produced. Accordingly, the applicants submit that the disclosure in the specification of two different antibodies, M69 and M123, that bind to the two-chain form of human matriptase without binding to the single-chain form of matriptase provides a representative number of species within the genus of the claimed invention in satisfaction of the requirement for written description under 35 U.S.C. §112, first paragraph.

The specification describes and characterizes the two-chain form of human matriptase in structural and chemical terms, and demonstrates that the two-chain form of human matriptase is structurally and functionally distinct from the single chain form of matriptase, as evidenced by the inability of the single-chain form of matriptase to form a complex with HAI-1, and the fact that the single-chain form of matriptase does not possess proteolytic activity. Since the application characterizes the antigenic two-chain form of human matriptase in chemical and structural terms that permit it to be clearly distinguished from the single-chain form of matriptase and from other proteins, and further describes two working examples of antibodies that bind to different structural features of the two-chain form of human matriptase and do not bind to the single-chain form of matriptase, the application satisfies the written description requirement of 35 U.S.C. §112, first paragraph, for claims 16, 18, and 34-36, directed to antibodies that bind specifically to the two-chain form of human matriptase.

V. CONCLUSION

For at least the reasons discussed above, it is respectfully submitted that the description of the claimed invention provided by the application satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for rejected claims 16, 18, and 34-36.

For the above reasons, Appellants respectfully request this Honorable Board to reverse the rejection of the claims.

Respectfully submitted,

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VI. APPENDIX – CLAIMS ON APPEAL

16. An isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human.

18. The antibody or immunologically reactive fragment thereof of claim 16, wherein the antibody is a monoclonal antibody.

34. The antibody or immunologically reactive fragment thereof of claim 16, wherein the immunologically reactive fragment is selected from the group consisting of scFv, Fab, Fab', and $F(ab')_2$.

35. The antibody or immunologically reactive fragment thereof of claim 16, wherein said single-chain form of matriptase comprises a polypeptide encoded by the nucleotide sequence of SEQ ID NO: 4, and the two-chain form of matriptase is produced by cleavage of said single-chain form of matriptase.

36. The antibody or immunologically reactive fragment thereof of claim 16, which binds to the two-chain (active) form of a matriptase protein that is present in a complex comprising Hepatocyte growth factor activator inhibitor-1 (HAI-1) or a fragment thereof.